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Original communication

Osmium impregnation detection of pulmonary intravascular fat in sudden death: A study of 65 cases

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ABSTRACT

Pulmonary fat embolism is widely recognised in forensic pathology. Pulmonary fat embolism requires mobilisation of free fat, entry of free fat into the circulation and lodging of fat globules in fine venous capillaries. This paradigm of fat embolisation has been used to support the evidence of antemortem fat depot disruption when the presence of intravascular fat is confirmed at autopsy. However, sporadic reports of intravascular fat in various medical conditions, which contradict the above mechanism, have opened questions about the alternative pathogenesis. In this study, 65 cases of sudden deaths were examined for the presence of pulmonary intravascular fat (PIF) by osmium impregnation. Cases were selected based on the criteria that were designed to eliminate the possible confounding effect from medical intervention or postmortem changes. Slides were graded based on their ease of search and only the fat droplets confined by the blood vessel or capillary wall were considered as a positive finding. The results show surprisingly high PIF incidences of varying degrees in all the categories of sudden deaths. Further study is needed to devise criteria for diagnosis of fatal fat embolism since the histological appearance of the high-grade PIF in natural sudden death may not be easily distinguishable from the traumatic fat embolism.

1. Introduction

There are certain findings at the postmortem examination which allow pathologists to deduce the perimortem events. One of such findings is the histological detection of fat globules lodged in the fine capillaries in the lung. The finding is referred to as a pulmonary fat embolism (PFE) and it is commonly accepted that the finding represents the antemortem disturbance to the fat depot while circulation is still intact. The first description of pulmonary fat embolism appears in a book by Zenker in 1862 where a massive fat embolism was noted in the lungs of a railway worker who was crushed to death.[1] It was postulated that the fat released from the bone marrow and adipose tissues by trauma was captured by the peripheral venous capillaries and then redistributed to the lungs by the systemic circulation.[2,3] Many case reports supporting this mechanism of fat embolisation were published as a case series from war casualties or traffic accident victims.[3–10] Experimental studies in animals confirmed the embolisation of fat globules from the bone marrow to the lungs via the systemic circulation.[11–14]

In general, the reports of fat embolism in the literature could be classified by the source of the fat globules. The first group of cases has bone marrow as the source of fat. The fatty composition of the marrow and the rich vascular connections make disruption of the bone marrow as the most likely source of the fat emboli. Along with traumatic fractures of the long bones, decompression sickness,[15–19] external cardiac massage,[20–22] sickle cell crisis[23–29] and osteomyelitis[30] all have been reported to have the PFE as secondary presentation. In addition, there are countless reports and experimental studies showing PFE as the complication of the orthopaedic surgery.[31–36] Another major source of the PFE reported in the literature is the liver. As the primary organ of lipid metabolism, failure of the lipid processing in the liver could lead to hyperlipidaemia and disseminated fat embolism. The liver has been implicated as the source of fat in the PFE cases with carbon tetrachloride poisoning,[37,38] fatty liver,[39–42] viral hepatitis[43–45] and abnormal lipid metabolism.[46,47] Even though it is rare, the introduction of the external lipid should also be recognised as the possible mechanism of the PFE. Historically, the PFE cases following oil contrast lymphography,[48–53] and parenteral nutrition[54,55] have

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been reported. Other rare causes of the PFE includes the disruption of adipose tissue in abdominal surgery[56] and liposuction,[57–64] and in the background of septicaemia that liberates free fatty acids from lipoproteins.[65–68] All of these above cases share three main factors: mobilisation (or introduction) of free fat, entry of fat into the circulation and lodging of fat in venous capillaries of the lungs.

Another way of classifying the PFE cases is to classify the mechanism of the fat mobilisation. The majority of the cases have a mechanically disrupted fat source and they follow the classical pathomechanism of traumatic PFE. Biochemical alterations of the chylomicrons by various lipases have been proposed as the alternate fat liberation mechanism and experiments in animals agree with such a hypothesis.[26,69–72] Even though the triglyceride content in chylomicron fat globules could be distinguished from the true fat globules by biochemical analysis,[73] the routine lipid stains typically used in the histological examination cannot show the difference between the different types of fat.[74,75] It is also important to note that no disruption of the fat depot is needed for this non-traumatic mechanism and the diagnosis of PFE could easily be missed without histologic examination for the fat. The initial case reports of uncommon PFE in the literature are summarised in Table 1. Perhaps the most interesting set of reports of the findings of PFE includes those that presumably occur after death.[76–79] Since the systemic circulation could not have been the vector for the fat globules, the findings of the fat in pulmonary vessels leave three possibilities: (1) existence of fat in pulmonary vessels in otherwise healthy/normal individual; (2) generation of fat *in situ*; and (3) other non-systemic circulation of fat by heat/pressure/gravity. Not much is known about the pathogenesis of pulmonary intravascular fat (PIF) without a clear fat source or systemic circulation, that is, a non-embolic mechanism.

In this study, cases of forensically significant sudden deaths were investigated for the presence of intravascular fat by osmium impregnation. In some of the cases in this study, both traumatic and non-traumatic, previous reports have demonstrated the presence of fat droplets. In other cases in this study, however, no previous reports of PFE exist. The selection criteria were designed to eliminate the following potentially confounding variables: resuscitation attempts that could have caused rib fractures, and signs of decomposition that could have altered lung morphology and mobilised the fat from the depot. The study included a group of cases of entirely benign sudden deaths that the traditional mechanism of embolism could not apply. Therefore, all the findings of fat globules within the pulmonary vasculature were simply termed as PIF instead of PFE.

Table 1
Summary of atypical PFE cases in literature.

Author, Year	Title
MacMahon and Weiss (1929)[37]	CCl_4 Poisioning with macroscopic fat in the pulmonary artery
Vance (1945)[93]	Intrauterine injection of Lysol as abortifacient
Durlacher et al. (1958)[39]	Sudden death due to pulmonary fat embolism in chronic alcoholics with fatty liver
David and Reinmann (1960)[76]	Pulmonary fat embolism and intravenous fat after local postmortem burning of the lungs
Clay (1963)[15]	Histopathology of experimental decompression sickness
Cuppage (1963)[94]	Fat embolism in diabetes mellitus
Bron et al. (1963)[48]	Oil embolism in lymphangiography. Incidence, manifestations, and mechanism
Hendrix and Fox (1964)[46]	Relation of obesity and abnormalities of lipid metabolism to lipid embolization of lungs
Charache and Page (1967)[23]	Infarction of bone marrow in the sickle cell disorders
Broder and Ruzumna (1967)[30]	Systemic fat embolism following acute primary osteomyelitis
Hay et al. (1968)[66]	Fatal fat embolism associated with disseminated tuberculosis
Sack and Wegener (1968)[77]	Artificial postmortem fat embolism
Groves et al. (1969)[67]	Hyperlipidemia and pulmonary fat embolism following *Escherichia Coli* bacteriaemia
Thomas and Tighe (1973)	Death from fat embolism as a complication of intraosseous phlebography
Barson et al. (1978)[54]	Fat embolism in infancy after intravenous fat infusions
Ross and Johnson (1988)[57]	Fat embolism after liposuction
Thienel et al. (1999)[95]	Fat embolism and hemorrhagic lupus pneumonitis in a patient with systemic lupus erythomatosus

2. Materials and methods

2.1. Selection criteria

Sequential cases of sudden death were selected for the study using the following criteria: (1) cases with evidence of resuscitation attempts (endotracheal tube or electrocardiogram (EKG) tabs *in situ*) were eliminated to exclude possible cardiopulmonary resuscitation (CPR)-related fractures leading to PFE and (2) cases showing any evidence of external or internal microscopic decompositional changes were eliminated as internal tissues liquefy and disrupt the tissue architecture. All cadavers were stored in low temperature before the autopsy to minimise the decomposition.

A total of 65 cases were selected (42 males, 23 females) representing the most common types of sudden deaths (Table 2): (1) sudden cardiac death (16 cases): the cases in this group include coronary atherosclerosis, hypertensive heart disease, acute myocardial infarct and ruptured myocardial infarct; (2) head trauma (14 cases): the cases in this group include blunt impact head trauma and gunshot wound to head; (3) asphyxia (22 cases): the cases in the group include hanging, drowning and positional asphyxia; (4) fire-related deaths (4 cases): the cases in this group include smoke inhalation and effects of fire; and (5) others (nine cases): the cases in this group did not belong to the previous four groups and include alcoholism with fatty change of liver (two cases), intracerebral haemorrhage (two cases), hypothermia (one case), ruptured atherosclerotic abdominal aortic aneurysm (one case), gagging with aspiration of gastric content (one case), cervical spine fracture (one case) and electrocution (one case). The mean age of males at the time of death was 49 years, whereas the mean age of females was 48 years.

2.2. Tissue sectioning/osmium impregnation/slide preparation

Lung tissues taken from autopsy were fixed in 10% formalin. Thin slices of lung tissue were taken systemically and post-fixed in osmium tetroxide solution (0.2% OsO_4 in 0.75% chromic acid) for 1 week for impregnation. After impregnation, tissues were processed in a Shandon Excelsior® tissue processor (Thermo Electron Corporation) for routine paraffin embedding. Processed tissues were then embedded in paraffin and cut using the microtome in successive sections to prevent the loss of the osmium-penetrated layer. Egg white albumin was used as an adherent to the glass slide and stained with haematoxylin and eosin.

2.3. Grading of PIF

In each case, two (2) slides showing the most surface area were selected for grading. Only uniform, round black-stained fat droplets within the blood vessels were considered as a positive finding. Severity of PIF was graded by the modified Mason's grading scale which uses the ease of searching under the microscope.[80] A score of

Table 2
Summary of cases used in this study along with their final Pulmonary Intravascular Fat (PIF) grade.

Age/Sex	Cause of death	PIF score
26/M	Coronary atherosclerosis with occlusive thrombosis in a man with acute methadone intoxication	0
56/M	Atherosclerotic and hypertensive heart disease	1.5
56/M	Atherosclerotic coronary artery disease with old myocardial infarction	0
65/F	Ruptured myocardial infarct with haemopericardium due to coronary atherosclerosis	0.5
65/M	Acute myocardial infarction due to coronary atherosclerosis with thrombosis	0.5
47/M	Atherosclerotic and hypertensive heart disease	0
53/F	Atherosclerotic coronary artery disease	0
48/M	Coronary atherosclerosis	0
51/M	Left haemothorax due to ruptured acute (localised) dissection of descending thoracic aorta	0
84/M	Ischaemic and hypertensive heart disease	1
49/M	Atherosclerotic and hypertensive heart disease	0
53/M	Atherosclerotic and hypertensive heart disease	0
47/M	Atherosclerotic heart disease (Diabetes mellitus)	0
55/F	Coronary atherosclerosis	0.5
57/M	Atherosclerotic heart disease in a man with epilepsy	1
50/F	Consistent with remote Myocarditis	0
65/M	Ruptured atherosclerotic abdominal aortic aneurysm with acute retroperitoneal haemorrhage	1.5
76/F	Acute intracerebral haemorrhage due to cerebral amyloid angiopathy	1.5
56/M	Intracerebral haemorrhage	0
74/M	Drowning in a man with hypertensive heart and atherosclerotic cardiovascular disease and acute alcohol intoxication	0
56/M	Drowning	0
20/M	Drowning	1
32/F	Drowning	0
61/F	Drowning	0
42/M	Fresh water drowning	0.5
84/M	Drowning	0
18/M	Hanging	1
31/M	Hanging	0.5
24/M	Positional asphyxia in a man with acute olanzapine intoxication	0
47/F	Hanging	0
39/M	Hanging	0.5
44/M	Hanging	0
23/F	Hanging	0
23/M	Hanging	0
50/M	Hanging	0.5
46/M	Hanging	0
55/M	Hanging	1
32/F	Hanging	0
35/F	Manual strangulation	2
36/F	Hanging	1.5
46/F	Hanging	0
42/M	Acute and chronic alcoholism	0
50/M	Chronic alcoholism	0
50/F	Acute ethanol toxicity (hypothermia)	1
84/F	Gagging with aspiration of gastric contents (postmortem burning) (Fig. 1)	2.5
38/M	Smoke inhalation and thermal injuries	1
61/F	Effects of fire	0.5
51/F	Effects of fire	1
69/F	Smoke inhalation	1.5
61/M	Intraoral gunshot wound	0
46/M	Close contact gunshot wound to head and brain	0
14/F	Blunt impact head trauma	1.5
51/F	Blunt impact head trauma with partial evisceration of brain	0
46/M	Gunshot wound of head evisceration brain	1
21/M	Gunshot wound to the head	1
32/M	Blunt impact head trauma	0.5
21/F	Blunt impact head trauma	0.5
45/M	Single close range gunshot wound to head and neck	0.5
68/M	Shotgun wound of head penetrating brain	3
40/M	Contact gunshot wound to head transecting brainstem	1
82/M	Near contact gunshot wound to the head	1.5
45/M	Intraoral gunshot wound	2
40/F	Gunshot wound to head	0
64/F	Fracture of cervical spine and cranium	1
56/M	High voltage electrocution	2

0 was given to the slides with no positive fat droplet and the highest score of 3 was given when positive fat droplets were present in large numbers. An intermediate score of 1 was given if the fat droplets were found after some searching, while a score of 2 was given when the droplets were easily found. Each slide was randomly graded using the above scale, and then an average of two slides was calculated for the final grade of each case.

3. Results

Table 2 summarises cases used in this study along with their final PIF grade. Of the 65 cases investigated, 34 cases showed some degree of PIF (52%). Table 3 compares the incidence of the PIF between sex, age groups and different causes of deaths. There was no difference of incidences between sexes as 22 out of 42 men (52%) were positive for the PIF, while 12 out of 23 women (52%) were positive. Cases from under 40 years old and over 65 years old had higher incidences than the cases between 40 and 65 years old (65%, 73% and 40% respectively). Of the cases with known antemortem fractures, 10 out of 14 cases (71%) were positive for PIF. PIF droplets found in sudden deaths (e.g., atherosclerotic heart disease) usually had diffuse distribution of fat globules, mainly involving capillaries and some involvement of larger venules.

4. Discussion

Before the origin of PIF can be discussed, it should be noted that it is assumed that no fat globules should be found in a normal living person who did not suffer from a recent injury. Both fat embolisation after injury to the fat depot and traumatic lipaemia can give rise to PIF but the fat droplets will normally be cleared by the phagocytic action of macrophages, emulsification with lipoproteins or other clearing mechanisms. Thus, postmortem findings of microscopic fat droplets occluding capillaries of the lung are widely believed to be indicative of recent injury.[80–83]

In this study, Mason's grading scale was modified to evaluate each slide by ease of search in a given field of view. While there are more quantitative and descriptive methods available for the grading of fat emboli,[84] this method allows qualitative grouping of slides of the same grade. This method is particularly efficient with osmium impregnation detection of the fat droplets since the technique is sensitive enough to show the diffuse distribution of small fat droplets which would pose a great challenge if quantitative grading was attempted. Also, osmium impregnation could be performed on formalin-fixed specimens, whereas other lipid stains require frozen sections for the best results.[74,75]

Table 3
The analysis of PIF incidences by sex, age group, and cause of death.

Sex	Male: 42 (22 positive)	Female: 23 (12 positive)	
Age	Under 40: 17 (11 positive)	40 to 65: 37 (15 Positive)	Over 65: 11 (8 Positive)
Cause of death	Cardiac: 16 (5 positive)	Asphyxia: 22 (9 Positive)	Other natural: 6 (3 positive)
	Fire related: 4 (4 positive)	Head trauma/GSW: 14 (10 positive)	Other violent: 3 (3 positive)
Total	34 positive for PIF out of 65 sudden deaths		

Table 3 summarises the findings of this study. Although it is not surprising to find fat globules in traumatic sudden deaths, it is important to note that some degree of PIF was found in all the types of sudden deaths that represent the majority of the medico-legal case population. In fact, in this study using osmium impregnation, it showed a very high incidence of PIF in all sudden deaths (52%, 34 out of 65 cases). Since the previous studies showing the rate of PIF in cases of natural sudden deaths is exceedingly rare, the comparison is made on the rate of fat embolism among the patients of long bone fracture. In his study, Mason et al. claimed the rate of the fat embolism to be 63% among patients with long bone fractures.[80] Subsequent studies showed great discrepancy in incidences even among traumatic cases depending on the method of investigation and only one comprehensive study in all types of sudden deaths has been conducted to date that showed an incidence of 17%.[8,9,85–91] Most PIF found in this study were those of lower grade but showed diffuse distribution. This could mean that the fat mobilisation or generation was not complete to have larger vessels of the lung involved at the time of death and it is not directly linked to the natural disease process that leads to the terminal event.

Finding of PIF in natural deaths has been previously attributed to PFE, even though it is not entirely clear that the fat could have embolised to lung in some cases. In his book, Sevitt stated that PFE found in natural deaths are usually slight in degree and not found in capillaries without arterial pressure to force fat into capillaries.[81] While this is generally true, the photomicrographs shown in Fig. 1 show a high degree of PIF found in a woman who died of gagging followed by postmortem burning. It shows a high number of intravascular fat droplets in a diffuse manner. This histological presentation suggests that fat has been generated as either a terminal process or postmortem changes of blood other than putrefaction. It has been reported that postmortem cremation results in fat embolisation.[76] All four cases of fire-related deaths in this study showed some degree of PIF. It is also the first time that PIF was recorded in a deceased who was electrocuted.

It is important to note that the incidence (but not degree or extent) of PIF in sudden deaths with significant tissue trauma is almost as high as those reported in long bone fracture patients with prolonged survival time (hours instead of minutes). Even though the presence of PIF in traumatic sudden deaths without marrow fat release is somewhat paradoxical due to the lack of time needed for fat migration, it has been recognised and studied in animal models. In his study, Suzuki et al. reported such violent sudden death cases but did not offer any alternative mechanism of fat generation and concluded that a high degree of PIF is almost a diagnostic marker of antemortem violence, irrelevant to survival time.[83] Other article have showed that a survival time of as little as 9 s is all that is needed for fat to travel to the lung in animal fracture models.[92] In this study, findings of high PIF incidences in sudden deaths with significant trauma suggest that the time required for fat embolisation in a human could be much less than previously thought and may simple require as little as the terminal spasms of heart.

Even though this study showed a high incidence of PIF among all types of sudden deaths, cases of chronic alcoholism with fatty changes of the liver did not show any PIF. This result does not confirm nor exclude the previous beliefs that the haemodynamics of the liver along with fatty changes of the liver should produce some degree of fat release into the venous system.[41–43,45] Also, the presence of high-grade PIF after postmortem burning refutes the belief that the presence of cardiac circulation is required for fat embolisation to the lungs. However, it is reasonable to assume that convectional current might have played a role in transferring fat globules mobilised by high heat.

PIF is one of many phenomena that may help pathologists to lay out the sequence of events that led to the death of an individual. No clear mechanisms, which could explain all possible different types of PIF, have been proposed at this time. This study raises questions about the occurrence of PIF in cases of sudden death. Prospective studies that include larger datasets would clarify the types of PIF that follow the current proposed pathogenesis and those that do not. Also, the presence of fat in the normal living population should be investigated to eliminate the possibility of PIF as normal features. At this time, it is apparent that there is more than one single mechanism that governs the process of fat mobilisation or generation. Of those cases that cannot be explained by the embolisation model, further studies should investigate: (1) the presence

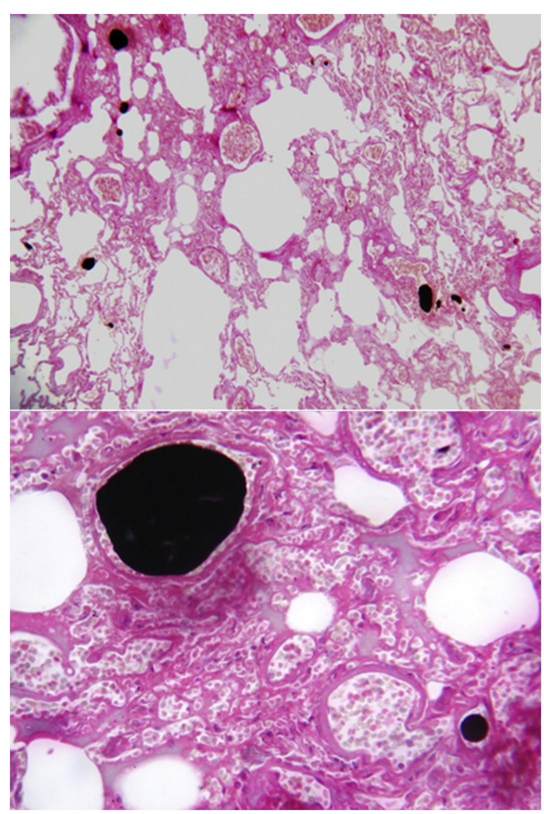

Fig. 1. Intravascular fat in lung. Osmium impregnation, H&E stain. Top: 25×. Bottom: 200×.

of other types of postmortem and perimortem fluid movement and (2) mobilisation of chylomicron fat by uncontrolled lipase activity.

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Conflict of interest

The authors hereby declare that they do not have any conflict of interest.

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